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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,358	MIGALY, PETER	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,41-43 and 48-143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,41-43 and 48-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This office action is a response to applicant's communication submitted July 22, 2009 in which claims 53, 84, 130, and 140-143 are amended and new claims 144-147 are introduced. This application claims benefit of provisional application 60/319436, filed July 30, 2002.

Claims 1-38, 41-43, and 48-143 are pending in this application.

Claims 1-38, 41-43, and 48-143 as amended are examined on the merits herein.

Applicant's most recent response contains numerous insults and hyperbole directed at the examiner, comparing the examiner to a conman, a psychopath, or a child abuser, and accusing the examiner of using pseudologic, discriminating against the applicant, victimizing the applicant, and subjecting the applicant to stress that is compared to battery, murder, or attempted murder, and which is described, in apparent seriousness, as a criminal act. According to 37 CFR 1.3, "Applicants and their attorneys or agents are required to conduct their business with the United States Patent and Trademark Office with decorum and courtesy. Papers presented in violation of this requirement will be submitted to the Director and will not be entered. A notice of the non-entry of the paper will be provided. Complaints against examiners and other employees must be made in correspondence separate from other papers." While the present response has been considered as is, Applicant is requested to abide by standards of decorum and courtesy in further communications with the office.

Again, Applicant is reminded:

An examination of this application reveals that applicant is unfamiliar with patent prosecution procedure. While an inventor may prosecute the application, lack of skill in this field usually acts as a liability in affording the maximum protection for the invention disclosed. Applicant is advised to secure the services of a registered patent attorney or agent to prosecute the application, since the value of a patent is largely dependent upon skilled preparation and prosecution. The Office cannot aid in selecting an attorney or agent.

A listing of registered patent attorneys and agents is available on the USPTO Internet web site http://www.uspto.gov in the Site Index under "Attorney and Agent Roster." Applicants may also obtain a list of registered patent attorneys and agents located in their area by writing to the Mail Stop OED, Director of the U. S. Patent and Trademark Office, PO Box 1450, Alexandria, VA 22313-1450

Applicant's amendment, submitted July 22, 2009, with respect to the objection to claims 6, 9, 10, 12,114-35, 37, 41-43, 48, 49, 51-56, 58-94, 96-107, 109-121, and 124-129 for containing underlining and strikethroughs in text that has not actually been inserted or deleted in the most recent amendment, has been fully considered and found to be persuasive to remove the objection as the claims are currently listed without the extraneous underlining and strikethroughs. Therefore the rejection is withdrawn.

Applicant's amendment, submitted July 22, 2009, with respect to the rejection of instant claims 140, 141, and 143 under 35 USC 112, second paragraph, for being incomprehensible, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to clearly indicate a therapeutic method involving additional steps wherein certain therapeutic considerations are discussed with the patient. Therefore the rejection is withdrawn.

Applicant's arguments, submitted July 22, 2009, with respect to the rejection of claims 127 and 128 under 35 USC 102(b) for being anticipated by Robertson et al., have been fully considered and found to be persuasive to remove the rejection as these claims are seen to specifically require that the antipsychotic be an atypical antipsychotic or dopamine system stabilizer, and furthermore the mention of sulpride, an atypical antipsychotic, in the reference is not seen to involve administration to patients having cognitive distortions. Therefore the rejection is withdrawn.

Applicant's amendment submitted July 22, 2009, necessitates the following new grounds of rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 140, 141, 143, and 144 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted March 13, 2009 with respect to the aforementioned claims has been fully considered and but is deemed to insert **new matter** into the claims since the specification as originally filed does not provide support for a method comprising discussing all of the specific considerations recited in the claims with a patient. Although the specification and the priority document 60/319436 do disclose these factors as considerations for physicians to take into account in the treatment of depression, they do not teach or disclose discussing them with a patient. As the instant specification as filed contains no description of this method the specification as originally filed does not provide support for the subject matter of instant claims 140, 141, and 143. See *in re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Because Applicant's amendment necessitated this new ground of rejection, the rejection is made **FINAL**.

The following rejections of record in the previous office action are maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 11-12, 37, 38, 41-43, 48-50, 53-71, 96-103, 126, 131-145, and 147 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal comprising administering certain antidepressants defined in the specification and prior art, does not reasonably provide enablement for such a method involving any antidepressant whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating depression and other disorders by administering a drug or a combination of two drugs. It is claimed that the antipsychotic drug improves the therapeutic outcome even in patients not suffering from psychotic symptoms.

The state of the prior art: Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art. Although a number of drug combinations have been tested and found to be useful, particularly combinations of a serotonin reuptake inhibitor with an atypical antipsychotic, many drugs of both types have not been tested. In particular, typical antipsychotics and dopamine system stabilizers such as aripiprazole have not been tested in the claimed methods. More generally, the full limits of the class of compounds known under the various functional groupings (e.g. selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, antidepressants with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, antidepressants with serotonin/norepinephrine/dopamine reuptake inhibition, etc.) recited in the language of instant claim 1 have not been determined, and it is likely that there exist novel compounds with antidepressant activity that have not yet been discovered.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The interaction between two classes of drugs is dependent on the specific mode of action of the two drugs. In the absence of any general theory explaining the action of atypical antipsychotic drugs to enhance therapeutic outcomes with antidepressants, it is not possible to predict the efficacy of any particular antipsychotic for this purpose absent experimental data. Because so many different compounds are known as antidepressants no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally. Thus the effectiveness of a

particular combination therapy of an antidepressant and an antipsychotic for the treatment of depression, cognitive distortions, smoking cessation, or nicotine withdrawal is unpredictable.

The Breadth of the claims: The claimed invention encompasses combination therapies of any of a number of functionally defined groups of antidepressants with an antipsychotic, particularly a typical antipsychotic, an atypical antipsychotic, or a dopamine system stabilizer. The antidepressants are defined only by their functional characteristics. In particular, a vast number of different structures are included within the limits of these claims.

The amount of direction or guidance presented: Two hypothetical cases are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-17)

The presence or absence of working examples: No working examples of the claimed therapeutic methods are provided by Applicant.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as antidepressant/antipsychotic combination therapy. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would be required to determine the extent of antidepressants useful in said methods. Because Applicant has provided no working examples, and because the state of the art is unpredictable, many different antidepressants would need to be tested in order to provide a comprehensive

understanding of which combinations are or are not useful in the claimed method. Because there is no structural limitation to the full scope of the various functionally defined groups of antidepressants, one skilled in the art would have to discover each and every possible compound with antidepressant activity. Doing so would require the synthesis and testing of an enormous number of compounds. In the process of synthesizing the compounds to be tested, many novel and unpredictable synthetic methods would have to be developed. These experiments would be repeated many times in animal models of depression, cognitive distortions, and nicotine addiction, in order to establish their suitability as therapeutic methods. It should be noted that evaluating psychological disorders such as depression and cognitive distortions in animals is more difficult than evaluating a therapy for a nonpsychological condition such as cancer or arthritis. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated many times, and involve the maintenance, killing, and disposal of many experimental animals, to establish the suitability or lack thereof for each compound found to possess the desired activity in vitro.

The scale of synthesis, *in vitro*, and *in vivo* testing described in the preceding paragraphs would present an undue amount of unpredictable experimentation to require of anyone wishing to practice the invention.

Genentech, 108 F.3d at 1366, sates that, “a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion.” And “patent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention with all of the compounds falling within the recited functional groupings of antidepressants.

Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that other issued US patents use the non-enabled terms and that therefore these terms should be given enablement for this application. However, each patent is treated on its own merits, and the fact that a particular term appears in an issued patent is not a valid argument in favor of its enablement in a completely different patent. Applicant also argues that the claims 140-143 are clearly enabled in a different way in the specification. These claims all depend from claim 1, and do not further limit the species of the antidepressant being used. They merely introduce additional steps involving consultation with the patient, which do not help one skilled in the art to obtain the needed combination of an antidepressant and an antipsychotic. Therefore they raise the same issues of enablement as the base claim.

Applicant further argues that the instant disclosure provides the successful conclusion of search that is necessary to warrant patent protection. However, Applicant's disclosure is not a disclosure of novel research on antidepressant and antipsychotic pharmacotherapy. Rather, by Applicant's own admission, it as a synthesis

of prior art elements. Therefore the facts disclosed by Applicant do not go beyond what is already known in the prior art. The only addition is a suggestion to combine prior art elements in a new manner. For Applicant's invention to be sufficiently complete and predictable for one skilled in the art to practice it, it must be predictable which antipsychotics can be combined with which antidepressants to achieve an augmenting effect. While Applicant's own teaching provides a suggestion for using various combinations of active agents, the enablement for such a combination will depend on what is known in the prior art about the utility of these drugs and their synergistic or antagonistic interactions. For combinations that have already been explored in the prior art, for example an atypical antipsychotic and a selective serotonin reuptake inhibitor, the combination can be enabled without further disclosure from Applicant. For other combinations, for example a combination of a typical antipsychotic and an NMDA receptor antagonist, the prior art does not give any reason to believe that the same augmenting effect would be present. Note that, while Applicant has provided a theoretical basis for synergism based on treatment of cognitive distortions, increased compliance, more rapid onset of action, and so forth, there is no concrete evidence that this mechanism is what is responsible for the observed augmentation effect of typical antipsychotics on selective serotonin reuptake inhibitors. If, for example, the augmenting effect is based on the actions of both of these drug classes on the serotonin neurotransmitter system, then the combination therapy would not work for antidepressants that do not affect serotonin, for example substance P antagonists or NMDA receptor antagonists.

Applicant further argues that actual working examples are not required for patentability and are prohibitively expensive for a small entity to undertake. Applicant gives the example of a small entity seeking patent protection for a spacecraft design. However, any idea that is sufficiently novel to warrant patent protection will require some sort of proof. The standard for enablement is not what the particular applicant can be expected to accomplish with his own limited resources but rather what scope of invention the public can be reasonably sure of having possession of in exchange for patent protection. In the case of a spacecraft, there would have to be a reasonable expectation that the spacecraft would actually function as described. Simply providing a spacecraft design whose functionality is unknown, (for example one that includes a novel type of engine that has never been successfully used) and asserting that the inventor does not have the resources to test it would not enable the spacecraft design. In the instant case, Applicant is claiming methods involving a wide variety of different antidepressants, many of which are not used in the prior art. Applicant's invention further depends on the augmentation of antidepressants by antipsychotic drugs without any clear teaching as to what factors are required for this augmentation to occur or whether it will really be present for any combination of an antidepressant and an antipsychotic regardless of the mechanism by which the two drugs work. Simply stating that two broad classes of drugs can by used together does not enable one skilled in the art to use them together if the results would be unpredictable.

Applicant further argues that the state of the art has shifted towards enabling patentability in the time since the filing of the invention. While Applicant has provided

examples (for example Reeves et al. included with PTO-1449) these examples are directed toward combinations of specific classes of drugs (for example a typical antipsychotic and a selective serotonin reuptake inhibitor) and are not seen in the prior art as applicable to all antidepressants or all antipsychotics.

For these reasons the rejection is deemed proper and made **FINAL**.

Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted January 8, 2007 with respect to claim 65 has been fully considered and but is deemed to insert **new matter** into the claims since the specification as originally filed does not provide support for the active metabolite of risperidone. As the instant specification as filed contains no description of said metabolite or a method of using it as a therapeutic agent, the specification as originally filed does not provide support for the subject matter of instant claim 65. See *in re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972).

Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the cited articles concerning grape juice are not relevant because they do not fit the facts of Applicant's analogy. Even disregarding whether grapes and grape

juice are identical, Applicant's analogy does not accurately represent the facts of the present case.

The analogy presented is that if grapes and grape juice were shown to have **the same effect**, then using grape juice would be inherent in using grapes. However, when this condition is attached to Applicant's arguments, this is not seen to be analogous for the situation of risperidone and its active metabolite. Administering an active metabolite is not necessarily the same as administering the precursor of said metabolite. The active metabolite could differ in its bioavailability, stability, shelf life, or rate of excretion, for example. Therefore the actual physiological effect of administering a given dose of the active metabolite of risperidone by a given route is not expected to be the same as the effect of administering the same dose of risperidone by the same route. The physical dosage form administered in each case would be a different composition of matter. Therefore the two methods are not identical and a disclosure describing one does not necessarily describe the other absent a specific description of both the parent drug and the active metabolite. Thus the rejection is deemed proper and made **FINAL**

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 11, 13, 37, 38, 41-43, 48, 49, 53, 54, 56, 58, 59, 119-121, 123, 126-129, 142, 145, and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howard. (US patent publication 2002/0123490, of record in previous action)

Howard discloses a combination of a serotonin reuptake inhibitor and an atypical antipsychotic, as well as a method for using this combination to treat obsessive compulsive disorder, psychosis, and depression. (p. 1, paragraph 0004) Depressive disorders treated include major depressive disorder, as well as atypical depression including anxiety. (p. 1, paragraph 0008) Anxiety is reasonably considered to be as cognitive distortion as it involves disordered cognitions such as overestimation of risk. Although treatment of refractory depression is a preferred embodiment, all depression including depression not found to be refractory, is included within the range of disorders to be treated. The amounts of each agent used are such that the combined effect has improved efficacy compared to either component individually. (p. 1 paragraph 0005) Atypical antipsychotics used in the invention include abaperidone, belaperidone, clozapine, iloperidone, olanzapine, perospirone, risperidone, sertindole, tiospirone, ziprasidone, zotepine, quetiapine, and blonanserin. (p. 7 paragraphs 0172-0198) The two agents are to be administered in dosages of about 5-200 mg/day of the antipsychotic agent and about 2.5-500 mg/day of the serotonin reuptake inhibitor. (p. 8 paragraph 0233) The compounds can be administered by various dosage forms including oral administration. (p. 9 paragraphs 0235-0236) Howard does not specifically disclose a method wherein the therapeutic agents are administered as soon as possible.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Howard as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Howard already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. Note that "as soon as possible" is an extremely broad limitation that would include practically any method wherein treatment was not deliberately delayed. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the reference would not be enabled for the purpose of the claims, specifically because Howard et al. discloses treating refactory depression as a preferred embodiment of the disclosure. However, the range of conditions to be treated is described as "depression, especially refactory depression." One of ordinary skill in the art would have understood this limitation as indicating utility for treating depression generally, and only including refactory depression as an especially preferred

embodiment. Preferred embodiments do not remove enablement for nonpreferred embodiments. One of ordinary skill in the art would have thus understood Howard et al. as teaching two embodiments, treatment of refactory depression and treatment of non-refactory depression. It would have been obvious to use the invention for either one of these categories individually.

Applicant further argues that it would not be obvious to administer the therapy of Howard et al. "as an initial treatment, as soon as possible, or upon presentation of said patient to a physician," because it would not in fact be indicated at said time due to clinical guidelines. Applicant further argues that the time frame for administration is further limited by the requirement that the depression be non-treatment-resistant. According to the definition in paragraph 0916 of the provisional application 60/319436, treatment resistant depression is defined as depression wherein the patient has had two unsuccessful courses of antidepressant therapy for six weeks each. Nothing in the disclosure of Howard or the other prior art would have made one of ordinary skill in the art determine that this therapy could not have been used as an initial therapy or a second therapy.

Applicant further argues that the present application reveals a new risk benefit analysis that is different from what is used in the art. Firstly, claims 140, 141, 143, and 144 as amended are now clearly directed toward a therapeutic method involving steps wherein the physisican discusses certain specific topics with the patient. Therefore these claims are no longer rejected as obvious over Howard et al., because one of ordinary skill in the art would not have had any reason from the reference to discuss

those specific topics. For the other claims, the claims are broad enough to encompass obvious embodiments. For example, “as soon as possible,” is interpreted to mean as soon as one of ordinary skill in the art would have considered the therapy to be a reasonable course of action. If, as alleged by Applicant, malpractice considerations would have kept one of ordinary skill in the art from using the therapy at a certain time, it is not “possible" to use it at that time, under the broadest reasonable interpretation of the claims. See the notes on claim interpretation below.

As regards the supposed new information disclosed by Applicant, the examiner, contrary to Applicant's allegation, has read the entire specification, as well as the provisional application 60/319436. The only new information provided consists of a recap of prior art knowledge about the treatment of depression and other psychiatric disorders, speculation as to how antipsychotics could improve certain contributing aspects of depression such as cognitive distortions which otherwise complicate its treatment with antidepressants alone, statements of opinion regarding the trade-off between the side effects of antipsychotic medication and its expected benefit in improving depression, and two hypothetical examples of how the invention would be expected to work if Applicant’s speculations are correct. None of these aspects are considered to be new information, as opposed to new opinions. Opinions are not patentable.

For these reasons the rejection is deemed proper and made **FINAL**.

Claims 1, 2, 4, 6, 10-15, 18, 22, 26, 30, 36-38, 41, 42, 48, 51-53, 56, 58-60, 109-118, 124, 125, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefson et al. '921 (US patent 5958921, of record in previous action, different from Tollefson WO99/61027 cited previously) in view of the Merck manual of diagnosis and Therapy. (Merck, of record in previous office action)

Tollefson '921 discloses a method of treating major depression comprising administering an effective amount of olanzapine. (column 1 lines 30-55) A dose of 2.5-30 mg per day is recommended. (column 2 lines 23-25) Olanzapine can be formulated as tablets for oral administration. (column 4 lines 5-25) Tollefson '921 does not disclose a method further comprising administering an antidepressant, for example one of the various serotonin reuptake inhibitors recited in the claims.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with olanzapine as disclosed by Tollefson '921. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Tollefson '921 as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Tollefson '921 and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer olanzapine in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that Tollefson et al. '921 is not enabled because the depressive patients not diagnosed as psychotic who are referred to in the patent and in the associated clinical

trial might possible be actually suffering from unrecognized psychosis. Applicant also speculates that no ethics committee would have approved the double-blind study referenced by Tollefson. All of these arguments are speculation by Applicant and to not provide any concrete evidence of non-enablement. An issued US patent is presumed to contain an enabling disclosure for, at the vary least, the subject matter of the issued claims. Proving non-enablement of an issued patent requires concrete evidence, not speculation that it is improbable that the invention actually works.

Therefore the rejection is deemed proper and made **FINAL**.

Claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, 109-122, 124, 126-130, and 140-143 are rejected under 35 U.S.C. 103(a) as being obvious over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action)

Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, a D4 receptor antagonist, (an antipsychotic) and a pharmaceutically acceptable carrier. (p. 1, left column, paragraph 0002) Note that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Phobias and panic disorders are also considered to be cognitive distortions. General types of antidepressants which can be used are listed in paragraph 0021 and include norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and monoamine oxidase inhibitors, among others, as

described in instant claims 11-13. Selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine, and sertaline. (p. 3, paragraph 0025) Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, as in instant claims 14 and 15. Other useful antidepressants are listed in paragraph 0181 on p. 8. The compounds used in this invention may all be administered orally, as described by instant claim 38. (p. 22, paragraphs 0460-0462) Various dopamine D4 receptor antagonists can be used, as listed on pp. 15-21. In particular, p. 20, paragraph 0446 lists olanzapine as a useful D4 receptor antagonist. D4 receptor antagonists can be administered in a preferred dose of about 5 to about 500 mg per day. (p. 22, paragraph 0459) Chappell et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider. Chappell et al. does not disclose a method where in the antipsychotic is administered in a dose of 2.5-10 mg olanzapine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Chappell et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Chappell et al. already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success

because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Chappell et al. using a dose of 5-10 mg of olanzapine per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Chappell et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Further, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that D4 antagonists are not necessarily antipsychotics. As discussed in the previous office action, Chappell et al. does not merely teach D4 receptor antagonists as a generic class. The reference also specifically exemplifies olanzapine, a known antipsychotic, which is explicitly stated in several claims such as claims 10, 18, 22, or

26 as being an embodiment of the claimed invention. The test for obviousness is not whether the reference discloses the same motivation as the prior art for practicing the claimed invention but whether it discloses any motivation for practicing any embodiment of the claimed invention. According to MPEP 2144, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. >See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings.");< In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991) Therefore it is not necessary that the prior art reference specifically disclose that the reason olanzapine works in this combination is because of its antipsychotic activity and not merely because of its D4 receptor antagonism.

Furthermore Applicant argues that Chappell discloses treatment of depression broadly without specifically excluding treatment resistant or psychotic depression. However, a broad teaching of utility for depression would be understood by one of ordinary skill in the art as including both treatment resistant and non-treatment-resistant

depression, as well as both psychotic and non-psychotic depression. Again, Applicant has given no reason to believe that the prior art's statement of depression in general is really meant to apply only to treatment resistant or psychotic depression.

Applicant additionally argues that the office action does not disclose whether the activity of olanzapine is due to its D4 activity. The test for whether the prior art teaches a particular element of the invention is whether or not it teaches that particular element, in this case a combination of olanzapine with an antidepressant. Whether or not the D4 antagonist activity is responsible for treatment of depression is not relevant.

Applicant further argues that anxiety and cognitive distortions are separate conditions and that anxiety is not a cognitive distortion. Applicant's argument for this position is, according to the previous response filed May 1, 2008, that anxiety is not always pathological, and that anxiety due, for example, to a totalitarian society or an abusive boss is rational and does not involve cognitive distortions. However, Chappell et al. specifically (on p. 1 paragraph 0010) defines anxiety as including anxiety disorders. Anxiety disorders are a pathological condition distinct from the reasonable feelings of anxiety experienced in adverse situations like those described. Applicant further argues that anxiety and cognitive distortions are not the same. However, all that is required for obviousness is that cognitive distortions are one element present in anxiety disorders. Even though anxiety disorders incorporate other elements besides cognitive distortions, the cognitive distortions are there and are an element of the disorder being treated.

For these reasons the rejection is deemed proper and made **FINAL**.

Claims 106-108, 131-134, and 136-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) in view of Berman et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine, which acts on the NMDA receptor, exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as the antidepressant in the method of Chappell et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the antidepressants recited by Chappell et al. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant has not provided any arguments specifically treating the combination of Chappell et al. with Berman et al. Applicant's arguments with respect to Chappell et al. alone are discussed above. Therefore the rejection is maintained and made **FINAL**.

Claims 5, 16, 17, 20, 21, 24, 25, 28, 29, 32-35, 64, 75, 76, 79, 80, 83, 84, 87, 88, 91-94, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Schmidt et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using ziprasidone, risperidone, or quetiapine as the antipsychotic agent.

Schmidt et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 198, table 1) In particular, ziprasidone, risperidone, olanzapine, and quetiapine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ziprasidone, risperidone, or quetiapine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant again argues that the reference does not disclose a link between antipsychotic activity and D4 receptor antagonism for the claimed compounds. This argument is dealt with in the rejection of Chappell et al. alone and is not found to be persuasive. Therefore the rejection is deemed proper and made **FINAL**.

Claims 5, 9, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Roth et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using risperidone, trifluoroperazine, or zotepine as the antipsychotic agent.

Roth et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 366, table 1) In particular, risperidone, olanzapine, trifluoroperazine and zotepine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use risperidone, trifluoroperazine, or zotepine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have

recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant has not provided any arguments specifically treating the combination of Chappell et al. with Roth et al. Applicant's arguments with respect to Chappell et al. alone are discussed above. Therefore the rejection is maintained and made **FINAL**.

Claims 1-3, 9, 11-15, 37, 38, 41-43, 48, 49, 53-62, 69-74, 96-105, 129, 142, and 145 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in previous action) as applied to claims 126-128 above, and further in view of the Merck Manual of Diagnosis and Therapy, Seventeenth Edition. (Reference of record in previous action, herein referred to as Merck)

Robertson et al. discloses a number of studies of the antidepressant activities of major tranquilizers (also known as typical antipsychotics). (p. 173, last paragraph) In particular, perphenazine and combinations of perphenazine with amitriptyline were used in treating patients suffering from depression, including non-psychotic depression. (p. 179, paragraphs 4-5) Perphenazine was found in one study to be particularly effective, while a combination of perphenazine and amitriptyline was found to be effective for treating other types of depression. It is noted that anxiety is reasonably considered to

be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Flupenthixol, (p. 183, paragraphs 4-6) and sulpride, (p. 185, paragraphs 1-2) are also seen to possess antidepressant activity. The intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, providing a neuroprotective effect, avoiding worsening of the depression, resisting suicide, avoiding suicidal ideation, and delaying or resisting relapse, are inherently present in any circumstance where the claimed drugs are administered to a patient suffering form depression, as all depressed patients are at elevated risk for suicide, and could suffer relapse after treatment. Robertson et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Robertson et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same

condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Robertson et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Robertson et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, submitted July 22, 2009, with respect to the above grounds of rejection, have been fully considered and not found to

be persuasive to remove the rejection. Applicant argues that the art developed a consensus against using antipsychotic drugs for treating depression. The evidence cited by Applicant appears to be the citation of a couple paragraphs in the specification that furthermore cite short passages from several prior art reviews. None of the cited documents (Nelson, Price, or Zimmerman) appear to have been included among the information disclosure statements submitted by Applicant. Based on Applicant's citation, it appears that the argument is that the art never recommended antipsychotic augmentation in non-psychotic depression because "the risk/benefit ratio … generally does not favor [antipsychotic augmentation]." This reflects a decision in the art, not that the previous evidence of antidepressant activity was absent or non-enabling, but that newer approaches worked better. The mere fact that a new approach is better does not thereby render an older, less effective approach non-enabled or non-obvious. It is still obvious, but it is simply not used.

Therefore the rejection is deemed proper and made **FINAL**.

Claims 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in previous action) in view of Berman et al. (Reference of record in previous action) The disclosure of Robertson et al. is discussed above. Robertson et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Robertson et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Robertson et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection, for reasons recited as regards the rejection over Robertson et al. in view of Merck above, and are not found to be persuasive for the same reasons.

Therefore the rejection is deemed proper and made **FINAL**.

Claims 1, 2, 4, 5, 6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48, 49, 51-64, 66, 70-77, 79-81, 83-85, 87-89, 91-105, 109-122, 124-129, and 145-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pivac et al. (Reference included with previous action) in view of Merck (Reference of record in previous action)

Pivac et al. discloses that atypical antipsychotics such as risperidone or olanzapine, should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph) Pivac et al. does not disclose a therapeutic method using the specific SSRIs fluoxetine, paroxetine, sertaline, or fluvoxamine, or the atypical antipsychotics ziprasidone or quetiapine. Pivac et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine. Merck et al. also discloses a listing of atypical antipsychotics, including clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone. (p. 1570, table 193-4)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the various SSRIs and atypical antipsychotics disclosed by Merck in the method of Pivac et al. One of ordinary skill in the art would have recognized that the specific compounds disclosed by Merck fall within the broad classes described by Pivac et al., and can thus be used in the disclosed method. Substituting these known prior art compounds in a known prior art method is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Pivac et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Pivac et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves.

Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant

reiterates the unconvincing line of argument regarding Ferris et al. from the previous communication. As discussed in the previous office action, Ferris et al. does not contain any teaching as to combination of antipsychotics with SSRI antidepressants, because SSRI antidepressants were not in common use at the time of publication. In any case, Applicant's statements regarding receptor profile are not relevant, because a finding of obviousness **does not depend on the prior art process working by a particular receptor**. Regardless of what mechanism the augmentation takes place by, it still falls within the limits of the claimed invention. Applicant's further arguments appear to rest on the assertion that his method has never been used before. However, this is flatly not the case, as Pivac et al. specifically discloses combining SSRIs and atypical antipsychotics for the treatment of depression. The only differences between this disclosure and Applicant's claims regard the use of specific SSRIs, and the timing and dosage of administration, which are routine in the art.

The papers cited by Applicant to substantiate his position do not actually suggest that Pivac et al. is not enabled. For example, Cremers et al. does not dispute the fact that 5-HT1A antagonists can augment SSRI antidepressants. (p. 13 right column last paragraph) The reference merely questions a particular theory as to how this effect happens. Roth et al. merely discloses that the effect of mianserin on 5-HT2 receptor binding is not due to an alteration in mRNA levels. Toth et al. comes to an opposite conclusion. Neither of these references suggests that atypical antipsychotics would not have an augmenting effect on SSRI antidepressants as described by Pivac et al.

Regarding Perez et al., the reference is not relevant to the instant case because it merely teaches that adding pindolol to a previously ineffective SSRI in treatment resistant patients does not reverse the treatment resistance. This teaching only concerns treatment resistant patients, and while it could be evidence against enablement of a method of treating treatment resistant depression, it does not give any clear teaching that could be applied to non-treatment-resistant depression.

The rest of Applicant's argument appears to be a bald assertion that Applicant's method is somehow different from the prior art, without any clear evidence.

Therefore the rejection is maintained and made **FINAL**.

Claims 1-4, 7, 8, 10-15, 19, 23, 27, 31, 36-38, 41-43, 48, 49, 51-63, 67, 68, 70-74, 78, 82, 86, 90, 95-105, 109-122, 124-130, and 145-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (PCT international publication WO02/060423, reference of record in previous action) in view of Merck. (Reference of record in previous action) Jordan et al. discloses a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor, comprising administering a compound having a given structure. (p. 15, lines 5-18) According to the Chemical Abstracts Registry entry 129722-12-9, (reference of record in previous action) this structure is aripiprazole. This compound is useful for treating various disorders of the central nervous system, for example major depression and melancholia, as well as various cognitive distortions including obsessive compulsive

disorder, alcohol and drug addiction, and cognitive impairment. (p. 16, line 23 – p. 17, line 10) The preferred unit dosage form is 1-20 mg of active agent. (p. 18, lines 5-10) Jordan et al. does not disclose a method comprising administering aripiprazole in combination with an antidepressant. Jordan et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering 2.5-15 mg of aripiprazole.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Jordan et al. to a patient suffering from major depression either alone or complicated by any of the various cognitive distortions recited by Jordan et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Jordan et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been

motivated to practice the invention in this manner because Jordan et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Jordan et al. using a dose of 2.5-15 mg of aripiprazole per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Jordan et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that one of ordinary skill in the art would not have been enabled for using aripiprazole in the claimed invention, because it was not approved and because it had not been used for treating cognitive distortions or treatment resistant depression, and further because the analogous compound buspirone is not used, either with FDA approval or off-label, to treat depression. The fact that those in the art do not use a particular therapy is not persuasive for a finding of non-enablement, as discussed below in the section "Further considerations". Regarding the reference Landen et al., as is the case earlier with Perez et al., the reference concerns treatment-resistant depression. The fact that a therapy does not work against treatment resistant depression does not prove it will not work against non-treatment resistant depression, as the very definition of treatment resistant depression specifies that it is more difficult to treat then ordinary depression, and not all therapies that are effective against non-treatment resistant depression will work against treatment resistant depression. What would be needed for evidence of non-enablement would be evidence that the combination does not work, or have any benefit over monotherapy, for the non-treatment-resistant depression that is treated in the instant claims.

Therefore the rejection is deemed proper and made **FINAL**.

Claims 106-108, 131-133, and 135-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (Reference of record in previous action) in view of

Berman et al. (Reference of record in previous action) The disclosure of Jordan et al. is discussed above. Jordan et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Jordan et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Jordan et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the examiner has not considered the reply to the third office action. Arguments raised with respect to Jordan et al. are discussed previously. Arguments relating to Berman et al. are discussed under "further comments" below.

Claims 3-5, 9-15, 20, 28, 37, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Theobald et al. (US patent publication 2003/0049308, first published as PCT international publication WO01/80837)

Theobald et al. discloses a transdermal or transmucosal patch comprising nicotine and a further active substance, that is useful for treating nicotine dependency, for nicotine substitution, or for disaccustoming smokers. (p. 1, paragraphs 0002, 0003, and 0009) The additional active agent can include antidepressants or neuroleptics (antipsychotics), for example chlorpromazine, perphenazine, sulpride, clozapine, clomipramine, doxepin, risperidone, paroxetine, or fluvoxamine. (p. 2, paragraphs 0015-0017) Theobald et al. does not explicitly exemplify a method comprising administering said patch comprising nicotine, an antidepressant, and an antipsychotic.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Theobald et al. using nicotine in combination with both an antidepressant and an antipsychotic. One of ordinary skill in the art would have been motivated to practice the invention in this manner because each of the additional agents (the antidepressant and the antipsychotic) is revealed individually by Theobald et al. to be useful in combination with nicotine for the treatment of nicotine addiction. Adding both of these agents at once to the disclosed invention is well within the ordinary and routine level of skill in the art and carries a reasonable expectation of success in achieving the desired therapeutic goal.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the reference is not enabling because paragraph 0008 rules out compositions with side effects. Presumably Applicant means by this that the patent would rule out using a neuroleptics because of the risk of extrapyramidal side effects, for example. However, this one paragraph should be taken in view of the later teaching in paragraphs 0015-0017 that neuroleptics can be used. Therefore one of ordinary skill in the art would read this reference as allowing the use of neuroleptics at a dose determined by one of ordinary skill in the art to be safe and well tolerated.

Furthermore Applicant argues that the lack of further disclosure of how the active substance (e.g. neuroleptic or antidepressant) treats the psychological nicotine dependency, and no other reference is given. However, in order to enable a disclosed method the reference need merely disclose how to make and use the disclosed invention. There is no requirement to disclose how exactly the invention works.

Therefore the rejection is deemed proper and made **FINAL**.

Further Comments

Difficulties in Argument and Claim Construction

As mentioned at the beginning of the office action, lack of knowledge of patent prosecution is usually a hindrance to prosecuting a patent. This is seen in the increasing number of claims in the application, and the confusing, disorganized nature of Applicant's responses, which have grown to over 200 pages in length, and which do

not properly address the actual issues on which the patentability of the claims depends. While Applicant is entitled to have any set of properly drafted claims examined on the merits, the manner in which Applicant has prosecuted this application makes it difficult to adequately consider and reply to every argument. Furthermore, Applicant demonstrates a lack of understanding of the standards of patentability and claim interpretation that guide the process of patent examination. Further explanation is given herein in the interest of expediting prosecution of this application. In response to Applicant's request for assistance in drafting allowable claims, the examiner does not see any allowable subject matter contained in the disclosure. Therefore it is not possible to draft allowable claims.

Claim interpretation

Each claim is interpreted on its own merits. Claims are only limited by the specification or other aspects of the disclosure when the disclosure explicitly defines a term appearing in the claim, or when the claim uses specific "means-plus-function" language as described in 35 USC 112, sixth paragraph. In all other cases, claim are given their broadest reasonable interpretation consistent with the prior art. For example a "method for treatment of a non-psychotic patient having cognitive distortions" as described in instant claim 3, encompasses any method wherein the claimed therapeutic agents (the antidepressant and antipsychotic) are administered to a patient having cognitive distortions. The scope of the claims are not limited only to what is discussed in the specification unless the specification clearly defines a particular term in a

particular manner. Therefore, although the specification describes cognitive distortions in the context of thought patterns that reinforce depression and complicate its treatment, other sorts of cognitive distortions, such as those occurring in patients suffering from anxiety disorders (e.g. overestimating risk, focusing on negative outcomes, overestimating the possibility of negative outcomes) also fall within the objective scope of the claims. Similarly, a phrase such as “as soon as possible" can be interpreted in many different ways, and therefore does not serve to significantly limit the scope of the claims.

Furthermore once the broadest reasonable interpretation of the claims is determined, the claim must be allowable over its entire scope to be allowable. That is, if the prior art anticipates or renders obvious any one embodiment of a claim, then the entire claim is anticipated or obvious. Similarly, for a reference to render a claim obvious, all that is necessary is that at least one obvious modification of the reference falls within the boundaries of the claim. For example, even if the prior art such as Chappell et al. teaches a number of different D4 antagonists, of which only one (olanzapine) falls within the claim limitations, that single embodiment can render the claim obvious even if the broad recitation (D4 antagonists) is not coextensive with the scope of agents (e.g. atypical antipsychotics) used in the claims.

Previous issued Patents

Applicant has repeatedly accused the Office of discriminating against small entities in favor of large drug manufacturers, pointing to various patents issued to drug

companies which allegedly should set a precedent that would lead to the allowance of the present claims. Firstly, the allowance of a patent does not set precedent. Examiners are bound by the Constitution, the Patent Act, the Manual of Patent Examining Procedure, and decisions by the Board of Patent Appeals and Interferences and the Federal courts. They are not bound by the decisions of other examiners in other applications, because the prosecution of each case is an independent process which depends on the specific fact pattern of the case. The mere citation of an issued claim in another application is not in itself an argument for the patentability of a similar claim in the present application without knowledge of the thought process that went into the allowance of said claim.

Applicant's Double Standard Regarding His Own and Others' Work

Applicant has repeatedly made the argument that others' publications and patent applications are not available as prior art against the present claims because they are non-enabling due to uncertainty or contrary teachings in the art, or due to regulatory and legal standards that would consider the methods taught in the prior art to be malpractice as they violate current clinical guidelines. These arguments are made despite the fact that all of the concerns raised by Applicant could be equally applied to his own claims. Applicant's disclosure does not introduce any new evidence or teachings over the prior art. The disclosure consists merely of a summary of the prior art uses of antidepressants and antipsychotics for treating depression and resisting suicide, and the suggestion that more aggressive treatment with the combination of these two drugs

would yield a clinical benefit in a reduced risk of suicide. Applicant's disclosure does not provide any new facts regarding antidepressant or antipsychotic therapy. It does not show any new benefit for this combination, but merely theorizes that treating cognitive distortions secondary to depression using an antipsychotic would improve the treatment of depression, and reduce the likelihood of the patient committing suicide before the antidepressant has time to work.

These arguments in the disclosure reflect Applicant's judgment as one skilled in the art regarding off-label administration of antipsychotic drugs, which is in fact a routine aspect of the current state of the art for treatment of psychiatric disorders. It is the case that those skilled in the art will prescribe antipsychotics off-label when they believe doing so is warranted, for example for treatment resistant depression. Applicant claims in his arguments that prescribing these drugs for non-treatment-resistant depression is malpractice and not enabled by the art. However, he also asserts that he is enabled for practicing the same method because of the new discovery disclosed in his application. This new discovery amounts to his personal judgment that the benefits of antipsychotics for augmenting antidepressant therapy are worth the risks. This is the same judgment used by any clinician prescribing a drug off-label, and if Applicant's judgment is sufficient to enable this off-label use, than the judgment of other clinicians in the prior art who suggest the combination of an antidepressant and an antipsychotic for initial treatment of depression is equally valid.

This pattern of argument is most striking as regards the enablement of treatments using ketamine. Applicant's specification provides no significant disclosure

of ketamine as an antidepressant. The only teaching regarding ketamine is its inclusion in a laundry list of antidepressants on p. 12 line 20 of the specification. In reciting ketamine in this manner, Applicant is relying for enablement on the fact that it is known in the prior art as an antidepressant, but relying for non-obviousness on the claim that one of ordinary skill in the art would not be able to use ketamine as an antidepressant. If ketamine were not known to have antidepressant properties in the prior art, its mere recitation in this manner would not be enabling. However, in response to the Berman et al. reference, Applicant argues that the hallucinatory and anesthetic effects of ketamine would prevent one of ordinary skill in the art from using it in place of other antidepressants disclosed in the prior art. (see p. 79 of Applicant's response filed 8/27/2007) If this were the case, then Applicant would also lack enablement for using ketamine as an antidepressant in the claimed methods, since he is basing his case for using it on exactly the same prior art teaching that are accessible to everyone else.

Standards of Patentability

Applicant's responses indicate a misunderstanding of the standards of patentability. 35 USC 102 states:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In other words, in order to be enabling, a patent disclosure must enable one skilled in the art to practice the invention. This is a separate requirement from the standards used by federal agencies regulating the use of certain inventions, such as the Food and Drug Administration, and is also distinct from the legal and ethical standards governing medical practice, and the standards used by peer-reviewed publications in the acceptance of articles for publication. There is no requirement that the invention be shown to be superior to the current state of the art, as is the case for FDA approval and avoidance of malpractice lawsuits. The only requirement is that the application place the public in possession of the invention, in exchange for exclusive patent rights to the invention for the patent term. Inventions which are immoral or illegal, or which are not commercially viable, for example, can still be patented. Patents to drugs which have never been approved by the FDA, or whose use has been discontinued due to safety concerns, are still valid patents and enabling for the purpose of anticipation or obviousness. For example, the non-steroidal antiinflammatory drugs rofecoxib (Vioxx®) or valdecoxib (Bextra®) have been withdrawn from the market because of adverse effects. In view of what is known about these drugs, administering them to a patient would constitute malpractice. However, if an applicant were to file a patent application claiming these compounds or their use as non-steroidal antiinflammatory agents, the patent would be rejected under 35 USC 102 and/or 103 as anticipated and/or obvious over prior art publications describing therapy with these drugs, even though no one

actually practices the methods described in the prior art at the present time due to safety and malpractice concerns.

In the instant case, a similar situation applies. Combinations of antidepressants and antipsychotics are known in the art but are not currently used in clinical practice as first-line therapy for depression because of concern over adverse effects, just as valdecoxib and rofecoxib are known to have non-steroidal antiinflammatory activity but are not used in clinical practice because of side effects. Publications exist (Howard et al., Chappell et al., Pivac et al.) describing using antidepressant/antipsychotic compositions. In order for a reference to be non-enabling, there must be a clear teaching in the art casting doubt on whether or not one skilled in the art would be able to practice it, not merely evidence that one skilled in the art would decide not to practice it. The question of whether or not to use antipsychotics as first-line treatment for depression is one of prudential judgment. For example, is the suffering of untreated depression more or less tolerable than the suffering caused by extrapyramidal side effects? Is a patient more likely to commit suicide due to untreated depression or due to drug-induced akathisia? Is a death from suicide more or less of a tragedy than a death from neuroleptic malignant syndrome? Is it morally preferable to take action that puts another's life in danger, or to refrain from action that could save their life? These are questions that cannot necessarily be answered by the teachings of the prior art. The decision of whether or not to use these drugs in this manner is not a settled scientific question which could render the prior art non-enabling, but simply the judgment of the majority of those skilled in the art, which has been codified in a set of guidelines.

Evidence of Secondary Considerations

Where an application claims an invention that is *prima facie* obvious over the prior art, but discloses new considerations that differentiate it from the prior art, the *prima facie* obviousness can be overcome and the invention patented. In order to prove a case of secondary considerations, the case must be supported with evidence that the present claims are somehow distinct from the prior art. For example, evidence that practicing the claimed invention produces an unexpected benefit not seen in the prior art.

Regarding evidence of unexpected results, according to MPEP 2145, "A showing of unexpected results must be based on evidence, not argument or speculation. In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997)" Applicant's disclosure presents no concrete data that the invention practiced as claimed (i.e. administering a combination of an antidepressant and an antipsychotic agent as first-line therapy for depression) produces any unexpected results. (e.g. reduced risk of suicide or suicidal thoughts) Evidence may be present in the specification as originally filed or introduced in a declaration under 37 CFR 1.132.

Regarding Applicant's arguments considering the need in the prior art for a solution to the paradoxical effect of antidepressants causing suicide, and the alleged failure of the art to propose a solution, the reference Reeves et al. (Included with PTO-1449) discloses a solution to this problem, through risperidone augmentation of antidepressant therapy. Unlike Applicant's unsupported speculation, the authors of this

publication provide actual evidence that the combination of risperidone and various antidepressants reduces suicidal ideation compared to the combination of an antidepressant and placebo. Therefore the prior art has in fact produced a solution to the problem of suicidality in patients taking antidepressants. Therefore others in the art have not failed to solve the problem that Applicant identifies.

More generally, evidence of secondary factors must include actual evidence that the claimed invention might solve the problems identified in the art, or succeed where others have failed. Applicant gives no basis in his disclosure for believing that his speculative line of reasoning would succeed where the art has failed to find a solution to the problem of suicidal ideation.

More generally, patent protection is granted in exchange for disclosure to the public of a novel, useful invention, not an unsupported idea. Many people can have a good idea but never reduce it to practice. A patent is granted to those who did the hard work and novel experimentation necessary to put the invention into practice. It is not granted for a mere speculation or suggestion to modify the prior art in a particular manner. While the disclosures of patent applications, including Applicant's own disclosure are given the benefit of the doubt as regards the enablement of the subject matter they describe, a higher standard is required when alleging secondary considerations. Applicant's disclosure does not meet those standards and cannot support secondary considerations to overcome a case of *prima facie* obviousness.

Conclusion

No claims are allowed in this application.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims

appealed. The Notice of Appeal must be accompanied by the required appeal fee of $250.00.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

/Eric S Olson/
Examiner, Art Unit 1623
8/28/2009

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623